BAROREFLEX SENSITIVITY ESTIMATION BY THE TRANSFER FUNCTION METHOD REVISED: EFFECT OF CHANGING THE COHERENCE CRITERION

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Abstract. **In this study we appraised three new criteria for the computation of baroreflex sensitivity (BRS) using the transfer function magnitude (TFM) method, with the aim of overcoming the conventional requirement of a coherence ≥ 0.5 between arterial pressure and RR interval time series. Measurements were carried out in a sample of 44 post-myocardial infarction patients at risk of malignant arrhythmias. The three proposed TFM criteria dramatically increased the number of measurable BRSs compared to the traditional coherence-based method and provided substantially equivalent BRS measurements. The agreement between these new indexes and BRS obtained by the phenylephrine test was similar to that of the traditional coherence method.**

Keywords – Baroreflex sensitivity, spectral analysis, transfer function

I. INTRODUCTION

Among the different spectral methods proposed so far for the estimation of baroreflex sensitivity (BRS) from spontaneous fluctuations of arterial blood pressure and RR interval, the one originally developed by Robbe *et al.* has gained wide acceptance due to the simplicity of the underlying physiological model, the easiness of implementation and the substantial linear association shown with measurements obtained with the classical phenylephrine technique [1, 2]. The method takes into consideration only non-respiratory oscillatory components in the so called low frequency (LF) band (0.04 Hz÷ 0.15 Hz), and implicitly assumes that RR fluctuations in this band represent the linear response of the baroreflex to corresponding fluctuations of systolic arterial pressure (SAP) plus a certain amount of uncorrelated noise (linear system, open-loop assumption). BRS is computed as the average value of the transfer function modulus (TFM), including only those points having a magnitude-squared coherence between SAP and RR ≥ 0.5 [1]. Although this criterion is usually satisfied in subjects having a well functioning reflex, in patients with cardiovascular diseases it is not uncommon to find no coherence values reaching the requested threshold. This is likely due to a low gain of the reflex and/or to a high disturbance on the RR signal compared to system input (i.e. SAP fluctuations). As a consequence, a large number of missing results are found just in those subjects in whom the detection of an impaired baroreflex is of greater important [3, 4].

We have recently shown by computer simulations that the behaviour of the "true" TFM can be approximated reasonably well by the estimated function even in conditions of coherence lower than 0.5, provided the analysis parameters (record length, type and width of spectral window) are appropriately chosen [5]. Moreover, reliable confidence intervals of the estimate can be computed in order to appraise the measurement error statistically [5]. On the basis of these findings we thought to define new criteria for the computation of BRS from TFM estimates. The aim of this study was to assess in a sample of pathological subjects the practical implications of these criteria in terms of rate of measurable BRSs, relationship between the new measurements and the traditional Robbe measurement and agreement with the standard invasive method (phenylephrine test).

II. METHODOLOGY

Subjects. We considered for the study 44 patients with a history of previous myocardial infarction (age: 61±9 years, LVEF: 37±11 %) admitted to the hospital for documented episodes of VT/VF or syncope of unknown origin. All these patients had a routine laboratory assessment of the autonomic function.

Experimental protocol. The experimental protocol included: 1) instrumentation and signal stabilization (15 min), 2) 8 min supine resting recording of ECG and noninvasive arterial blood pressure at the finger (Finapres 2300), 3) evaluation of BRS through the phenylephrine test (3 repetitions). The latter was administered according to the Oxford technique.

Signal preprocessing. RR interval (resolution 1 ms) and SAP time series were obtained from row signals. Ectopic beats were linearly interpolated. Recordings with an ectopy rate > 5% were discarded.

Baroreflex estimation: transfer function methods. Signals were visually inspected and the widest sub-record with all signals free from artifacts, large transients or marked changes in the fluctuating behavior of the signals was interactively selected. After linear detrending, bivariate spectral analysis between SAP and RR time series was

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Abstract

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performed using the weighted covariance method with a 0.03 Hz bandwidth Parzen window [5, 6]. The TFM, its 95% confidence interval and the coherence function were then obtained as previously described [5]. BRS was estimated averaging the TFM in the LF band according to four different criteria: 1) taking only those points having a corresponding coherence ≥ 0.5; 2) taking only those points having a 95% CI $\leq \pm 3$ ms/mmHg; 3) taking only those points significantly different from zero or non significantly different from zero and ≤ 3 ms/mmHg; 4) taking all TFM points without any restriction. The first criterion represents the straight application of the Robbe method. The second criterion aims at controlling the error by setting a "maximum acceptable" error in the TFM estimate. This is because the 95% CI is a statistical description of the range of the error. The third criterion is based on the notion of discarding those TFM values indicating a relatively preserved baroreflex gain (i.e. >3 ms/mmHg) which might be so by chance alone. Hence, statistical testing is used here as a means to protect against false negative results. The fourth criterion assumes that the random error of the TFM estimate, due to the erratic behavior of finite-length spectral measurements [6], can be partly filtered out by averaging over the entire LF band, approximating the "true" function. This , in turn, is based on the empirical observation that the bias of TFM estimates for sufficiently large record lengths (say ≥ 420 s) is negligible [5].

Baroreflex estimation: phenylephrine test. For the analysis of the phenylephrine test, RR intervals were plotted against the preceding SAP value, and a linear regression analysis was performed for those points included between the beginning and the end of the first significant pressure upstroke (≥ 15 mmHg). A final slope was obtained by calculating the mean value of three tests.

Statistical analysis. Comparisons among the four measurements of BRS using the different averaging criteria for the TFM were performed by ANOVA for repeated measurements. Linear correlation was assessed by the Pearson correlation coefficient. Results are expressed as mean±SD. The significance level was set at 0.05.

III. RESULTS

Fig. 1 shows two representative examples of BRS estimation through the TFM method. Upper tracings are the observed SAP and RR time series (i.e. the input and output of the system), while panel c shows their respective spectra superimposed (solid and dashed line respectively). Panel d displays the coherence function. Notice that in the example to the left a large portion of the coherence in the LF band is above the 0.5 threshold (dashed-dotted line), whereas in the second example it is always < 0.4. Hence, according the Robbe method, this patient will not have a measurable BRS. The TFM is shown in panel e with the LF band delimited by two vertical bars. Notice that in both examples the TFM exhibits a similar band-pass behaviour which is clearly supported by the behaviour of the 95% confidence interval (dashed lines). The latter also indicates that in the LF band the TFM is almost always significantly different from zero, implying that about all points of the TFM will be included in the computation of the BRS according to criterion 3 (see methods). Finally, panel f gives the behaviour of the bi-directional range of the error (half confidence interval), as a function of frequency. Since this range is <3 ms/mmHg, using criterion 2 for the computation of BRS all points of the TFM in the LF band will be included in the average.

Descriptive statistics of spectral BRS measurements according to the defined computation criteria are given in table I. In more than half of the patients the coherence did not reach the 0.5 threshold and BRS according to the Robbe criterion could not be measured. In the patients with a measurable BRS, the proportion of the LB band contributing to the measurement was on average about one third. The bi-directional range of the error within the LF band was 2.3±1.7 ms/mmHg. Using criterion 2, 95% of the patients had a measurable BRS which was estimated on average on 81% of the LF band. Using the third criterion, BRS could be measured in all patients and the average percentage of points included in the analysis was very high (97%). All modified TFM criteria yielded a very similar BRS which was slightly but significantly lower than that obtained with the Robbe method. The correlation coefficient between spectral indexes was very high ($r \geq 0.93$ for all pairwise relationships).

Table II shows the results for the comparison between BRS measurement obtained using TFM methods and the classical phenylephrine test. The correlation coefficient between phenylephrine BRS and Robbe index was slightly higher than between phenylephrine and the 3 modified TFM methods. This difference, however, was not statistically significant ($p>0.21$ for all comparisons). Indeed, restricting the correlation analysis to the 19 patients having the Robbe measurement, the correlation coefficients became quite similar (table III, $p>0.27$ for all comparisons). All modified TFM methods yielded slightly negatively biased results with respect to phenylephrine measurements (tables II and III). The limits of agreement were very similar in the traditional and modified TFM methods (tables II and III, $p >0.38$ for all comparisons).

IV. DISCUSSION

In this study we have appraised three modified versions of the TFM technique originally developed by Robbe and co-workers for non-invasive estimation of BRS, and have tested them in a population o post-MI patients at risk of malignant arrhythmias. We found that the Robbe index could be estimated in less than half of the patients and that only about one third of the LF band contributed to the measurements. Conversely, the modified TFM techniques included in the

average a much larger part of the band (from 81% to 100% on average) and allowed to estimate BRS in a percentage of patients varying from 95% (controlling for the range of the error) to 100% (checking the statistical significance of the estimate or including all points in the average).

BRS values obtained with the Robbe method were on average about 1.1 ÷ 1.4 ms/mmHg higher than those obtained with the modified criteria, this positive offset being the effect of including only those points at higher coherence, which are typically associated with higher TFM values. BRS measurements obtained with the modified TFM methods did not show any systematic difference and were highly correlated each other. This may have been caused by the fact that, in this dataset, all acceptance criteria selected most frequency components, the 3 ms/mmHg being the most selective one. The modified TFM methods were also highly correlated with the Robbe method.

BRS values obtained using modified TFM techniques do not seem to introduce any significant improvement/worsening in the agreement with phenylephrine test measurements compared to the Robbe method. Due to the observed large limits of agreement, the results of this study confirm previous findings in similar populations of subjects that the random differences between spectral and phenylephrine test estimates of BRS do not allow to use them interchangeably.

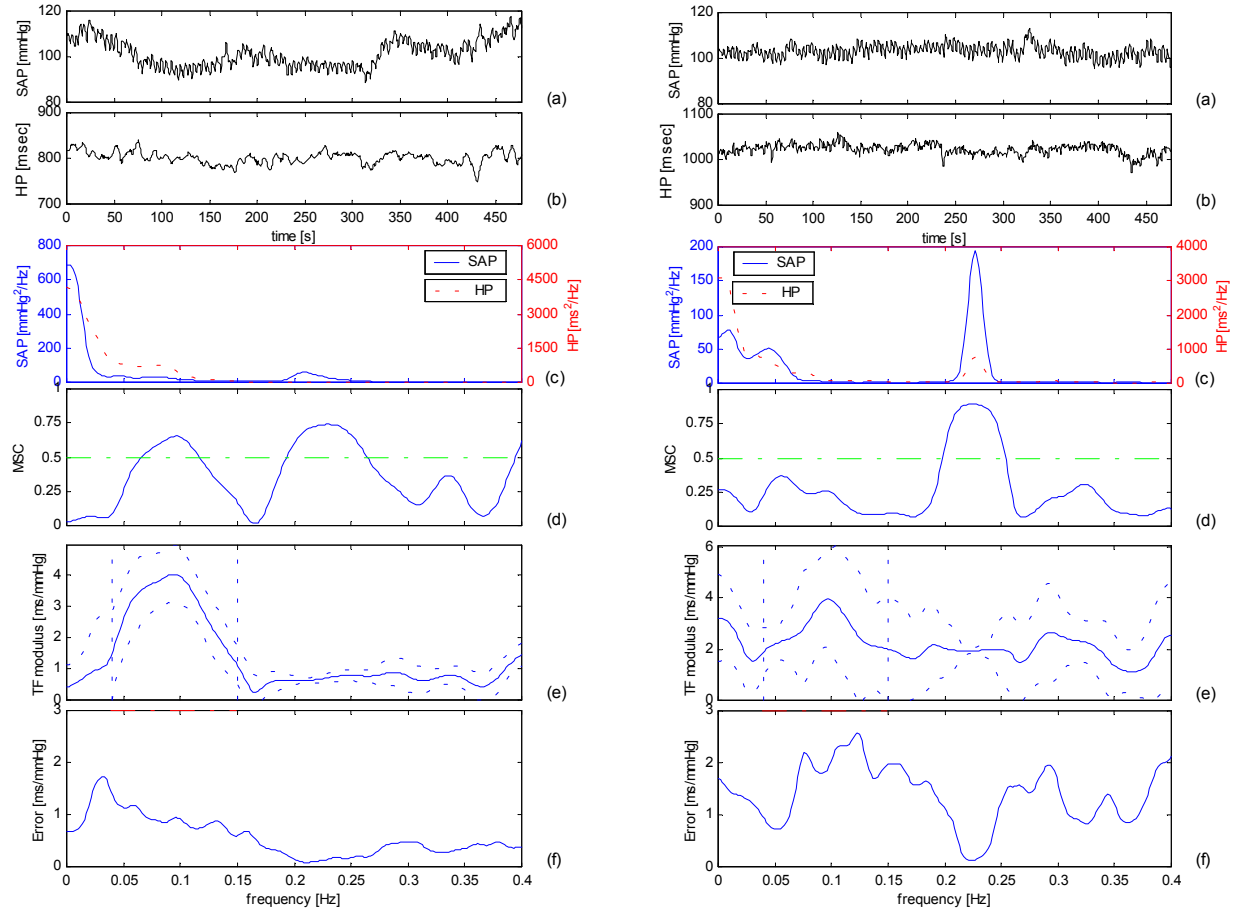

Fig. 1. Representative examples from two subjets of the study (left and right respectively). Panel (a): systolic arterial pressure (SAP) and (b) RR interval time series. Panel (c): autospectra of SAP and RR superimposed. Panel (d): Coherence function. Panel (e): transfer function modulus (TFM, solid line) with 95% confidence interval (dashed lines). Panel (f): bi-directional range of the error (half confidence interval), as a function of frequency.

TABLE I

BAROREFLEX SENSITIVITY (BRS) MEASUREMENTS BASED ON THE COMPUTATION OF THE AVERAGE TRANSFER FUNCTION MODULUS (TFM) IN THE LF BAND (0.04÷0.15 Hz) ACCORDING TO FOUR DIFFERENT ACCEPTANCE CRITERIA.

Acceptance criterion for TFM estimates	N	Contributing part of the band [%]	BRS all included cases [ms/mmHg]	BRS in the 19 cases passing the Robbe criterion [ms/mmHg]
Coherence ≥ 0.5 (Robbe)	19	32±24	5.4±3.8	5.4±3.8
Error ≤ 3 ms/mmHg	42	81±31	3.3±2.5	4.0±3.1*
Statistical significance	44	97±7	3.8±3.2	4.3±3.4*
All points	44	100±0	3.8±3.1	4.3±3.4*

N: patients satisfying the acceptance criterion. *) $p< 0.001$ compared to the Robbe criterion

TABLE II

COMPARISON BETWEEN BAROREFLEX SENSITIVITY (BRS) MEASUREMENT BY THE PHENYLEPHRINE TEST AND SPECTRAL MEASUREMENTS.

Acceptance criterion for TFM estimates	N	PHE BRS [ms/mmHg]	r	bias [ms/mmHg]	LoA [ms/mmHg]
Coherence ≥ 0.5 (Robbe)	19	5.5±4.1	0.75	- 0.1	±5.5
Error ≤ 3 ms/mmHg	42	5.1±3.8	0.63	-1.8†	±5.8
Statistical significance	44	5.2±3.8	0.63	-1.4†	±5.9
All points	44	5.2±3.8	0.63	-1.4†	±6.0

PHE BRS: BRS measured by the phenylephrine test; r= correlation coefficient; LoA= limits of agreement.

†) $p< 0.01$ testing the null hypothesis bias=0.

TABLE III

COMPARISON BETWEEN BAROREFLEX SENSITIVITY (BRS) MEASUREMENT BY THE PHENYLEPHRINE TEST AND SPECTRAL MEASUREMENTS IN THE SAME SUBGROUP OF PATIENTS HAVING ALL SPECTRAL MEASUREMENTS.

Acceptance criterion for TFM estimates	N	Correlation Coefficient	bias [ms/mmHg]	LoA [ms/mmHg]
Coherence ≥ 0.5 (Robbe)	19	0.75	- 0.1	±5.5
Error ≤ 3 ms/mmHg	19	0.64	-1.5†	±6.3
Statistical significance	19	0.69	-1.2	±5.9
All points	19	0.69	-1.2	±5.9

†) $p=0.05$ testing the null hypothesis bias=0.

REFERENCES

[1] H.W.J. Robbe, L.J.M. Mulder, H. Ruddel, W.A. Langewitz, J.B.P. Veldman and G. Mulder, "Assessment of baroreceptor reflex sensitivity by means of spectral analysis", *Hypertension,* vol. 10, pp. 538-543, 1987

[2] R. Maestri , G.D. Pinna, A. Mortara, M.T. La Rovere, L. Tavazzi, "Assessing baroreflex sensitivity in post-myocardial infarction patients: comparison of spectral and phenylephrine techniques", *J. Am. Coll. Cardio.l,* vol. 31(2), pp. 344-351, 1998

[3] C.A. Swenne, J Frederiks, P.H. Fisher, W.F.C. Hardeman, M.A.C. Immerzeel-Geerlings, B.J. Ten Voorde, "Noninvasive baroreflex sensitivity assessment in geriatric patients: feasibility and role of the coherence function", Computers In Cardiology 2000; 27:45-48, 2000

[4] R. Colombo, G. Mazzuero, G. Spinatonda, P. Lanfranchi, P. Giannuzzi, P. Ponikowski, A.J.S. Coats and G: Minuco, "Comparison between spectral analysis and the phenylephrine method for the assessment of baroreflex sensitivity in chronic heart failure", *Clinical Science*, vol. 97, pp. 503-513, 1999

[5] G. D. Pinna, R. Maestri, "Reliability of transfer function estimates in cardiovascular variability analysis", *Med. Biol. Eng. Comput*., 2001, in press

[6] M.B. Priestley, "'Spectral analysis and time series", Academic Press, London, 1981: